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PENICILLIN RESISTANCE AMONG INVASIVE PNEUMOCOCCAL ISOLATES AT 10 CHILDREN'S HOSPITALS, 1991-1994

Introduction

Streptococcus pneumoniae is an important human pathogen, noteworthy for its roles in otitis media, pneumonia, bacteremia, and meningitis. While it was once uniformly susceptible to penicillin, this is no longer a safe assumption[1]. Isolates relatively resistant to penicillin (with minimum inhibitory concentrations [MICs] from 0.10 to 1.00 µg/mL) have been detected for decades[2] but such resistance has impaired treatment responses only in certain clinical conditions, such as meningitis[3]. The prevalence of relatively resistant isolates has increased rapidly during the past decade in many countries[1]. High-level resistance to penicillin (MIC ≥ 2.0 µg/mL) has also emerged among pneumococci and is becoming more common in many areas[1,4]. Such isolates are often resistant to multiple antibiotics[1] and can pose therapeutic challenges[5].

A recent report from Toronto indicated that 20 of 274 pneumococcal isolates (7.3%) tested were penicillin-resistant; 6 (2.2%) at high levels[6]. Resistant strains have also been encountered in Quebec[7]. These reports raise questions about the extent of the problem elsewhere in Canada. The hospital-based active surveillance network called the Immunization Monitoring Program, Active (IMPACT) has been collecting information about pneumococcal isolates at 10 pediatric centres since 1991. This report provides preliminary data on the penicillin susceptibility of over 900 isolates.

Methods

The organization of IMPACT has been described previously[8]. The 10 participating hospitals are distributed countrywide and include about 80% of Canada's tertiary care pediatric beds. This survey started early in 1993 and included retrospective case reviews for 1991-1992 and prospective case documentation through 31 December 1994. Cases were selected in a uniform fashion, from hospital discharge diagnoses and laboratory records, for all 4 years of the survey. Nurse monitors at each centre abstracted case information on a form designed for this purpose. Case reports were collected and analyzed at a coordinating centre.

The case definition of invasive infection required isolation of *S. pneumoniae* from blood, cerebrospinal fluid or other normally sterile sites. All participating centres routinely screened invasive isolates for penicillin resistance using a Kirby-Bauer oxacillin (1 µg) disk method. Laboratories used various criteria to select isolates for determining MICs of penicillin. Chosen isolates usually included those resistant in the screening tests. Laboratory methods were not standardized among centres.

The study was approved by the institutional review boards of each centre.

Results

In total, 955 isolates were identified; 922 (97%) were tested by oxacillin screening and 344 (36%) by penicillin MIC determination. The proportion of isolates screened increased progressively from 94% in 1991 to 99.6% in 1994. Two centres in Montreal and one in Ottawa accounted for 98% of tests done. Most centres did MIC determinations only on isolates positive in the screening tests.

Test results are summarized in Table 1. The prevalence of oxacillin-resistant isolates was 2.8%, with no clear temporal trend. Among the 344 isolates further tested, intermediate penicillin resistance (MIC 0.10 to 1.0 µg/mL) was present in 15 and high-level resistance (MIC ≥ 2.0 µg/mL) in four isolates. The highest observed MIC was 2.0 µg/mL. Isolates with high-level penicillin resistance were seen more often in 1994 (three isolates)

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Table 1
Results of tests for penicillin resistance in pneumococci at hospitals participating in IMPACT

Year	Total Isolates	Oxacillin Screening Test		Penicillin MIC µg/mL			
		No. Resistant/No. Tested	%	No. Tested	< 0.10	0.10 - 1.0	≥ 2.0
1991	233	4/219	1.8	78	75	3	0
1992	263	9/252	3.6	93	86	6	1
1993	225	3/218	1.4	72	71	1	0
1994	234	10/233	4.3	101	93	5	3
TOTAL	**955**	**26/922**	**2.8**	**344**	**325**	**15**	**4**

than in the 3 earlier years combined (only one isolate in 1992, $p = 0.04$, Pearson's chi-square). All four highly resistant isolates were from Montreal. The Montreal centres also accounted for 12 of the 15 isolates with intermediate resistance. Single instances of intermediate resistance occurred in Quebec, Ottawa, and Toronto.

Of the 26 isolates resistant to oxacillin, 18 were tested to determine the penicillin MIC. Sixteen had intermediate or high-level penicillin resistance. Two were susceptible to penicillin.

An additional three isolates from the study had intermediate penicillin resistance although they were sensitive to oxacillin. Their MICs ranged from 0.12 to 0.30 µg/mL. They were identified in laboratories routinely performing oxacillin screening and penicillin MIC testing on all isolates.

Comments

This multi-centre survey provides a timely indication of penicillin resistance rates among pneumococci isolated from children with invasive infections. The size of the case series and its nationwide scope increases its validity. However, the data should not be applied to localized infections in children (such as otitis media) or to infections in adults because different populations of pneumococci may be involved, with different rates of resistance[1].

Reporting laboratories are located in university hospitals and take part in annual accreditation tests. Although susceptibility data came from tests routinely performed at participating centres, test methods were not standardized among these centres. The regularity with which isolates were screened for resistance varied minimally among centres and increased from 94% in 1991 to 99.6% in 1994. In the absence of any central directive regarding screening, it is reassuring to note that all centres automatically performed regular oxacillin screening of invasive isolates as early as 1991 or before. The value of the oxacillin screening test is in its ability to predict reduced penicillin susceptibility. This test is very sensitive but less specific. Up to 14% of strains that have oxacillin zone sizes < 20 mm may prove to be susceptible to penicillin, usually exhibiting borderline MICs of about 0.06 µg/mL[9]. Our finding of 11% (two of 18) of isolates showing this discrepancy is consistent with the published data. The oxacillin screening test rarely fails to detect reduced penicillin susceptibility. No such strains were detected in a study that examined 248 isolates[9]. Discovering three such strains in 344 was therefore unexpected. This could be due to a lack of standard laboratory methods in performing this screening test or a previously undetected error rate in the test. Our isolates have been recovered from storage and are being retested at the National Centre for Streptococcus in Edmonton. This will help standardize screening and susceptibility tests nationally as well as clarify the rate of penicillin resistance in the full collection of isolates.

Pneumococci with intermediate or high-level resistance to penicillin were infrequent. Among over 900 screened isolates, 2.8% were oxacillin-resistant. Confirmatory testing was not done in every instance but 15 isolates had intermediate penicillin resistance (1.6% of screened isolates) and four had high-level resistance (0.4% of screened isolates). No temporal trend was evident in the prevalence of strains with intermediate resistance, which was similar to the reported rate of 2.4% in Alberta in 1974-1976[2]. Too few highly resistant strains were encountered to reliably discuss any temporal trend. However, the rate observed in 1994 was significantly higher than that in the preceding 3 years ($p = 0.04$, Pearson's chi-square). Rapid increases in the prevalence of resistant isolates have been observed in areas of the United States[4], indicating the potential for greater problems in Canada.

The majority of resistant isolates in this survey came from Montreal. All four highly resistant isolates were obtained there, along with 12 of 15 strains with intermediate resistance. The remaining resistant isolates came from other centres in central Canada but some were also detected in Calgary. The case distribution may have been influenced by the thorough testing carried out in the Montreal centres, but more likely it indicates that resistant pneumococci are more prevalent in that area, as earlier reports have indicated[7]. A similar situation exists in Toronto[6], but there the isolates were not limited to children.

For clinicians, the fact that high-level resistance has been documented in pneumococci in Canada is more important than their exact prevalence or geographic distribution. The potential exists for any new case to involve resistant organisms. This possibility should be anticipated in the management of children with life-threatening pneumococcal infections[5]. This should include routine susceptibility screening of all pneumococci isolated from blood, spinal fluid or other normally sterile sites, followed by penicillin MIC determination on isolates found to be resistant in the screening. The situation also indicates the necessity of continued nationwide surveillance with prompt infection control measures.

Acknowledgements

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Source: *D Scheifele, MD, BC's Children's Hospital, Vancouver; R Gold, MD, MPH, Hospital for Sick Children, Toronto; V Marchessault, MD, Canadian Paediatric Society, Ottawa; J Talbot, MD, PhD, National Centre for Streptococcus, Edmonton; and Members of the LCDC/CPS IMPACT Group.*

Editorial Comment

Streptococcus pneumoniae with diminished susceptibility to penicillin is becoming a concern for public health officials and clinicians worldwide. While several Canadian centres report rates of penicillin-resistant pneumococci < 10%, at least one large American city reported a rate of 25% in 1994[1]. The IMPACT network is unique in providing ongoing information about penicillin-resistant pneumococci across the country. This study examines the penicillin susceptibility of 955 sterile-site pneumococcal isolates taken in children < 5 years old in the 10 participating Canadian hospitals. During the period 1991-1994, it reported rates of intermediate penicillin susceptibility and resistance of 1.6% and 0.4%, respectively. These data, combined with results currently being collected from patients of all ages as part of LCDC's Sentinel Health Unit Surveillance System, will clarify the national situation with respect to *S. pneumoniae* with diminished susceptibility to penicillin. This should compliment similar data being collected worldwide.

The emergence of penicillin-resistant pneumococci should encourage the use of existing polysaccharide pneumococcal vaccines in recommended populations. A new generation of protein polysaccharide conjugated vaccines, immunogenic in young children, is being developed which will provide an additional preventative intervention. Surveillance networks such as IMPACT have the added advantage of being able to monitor, nationally, the serotype distribution of *S. pneumoniae*. Though not reported here, these data will help to predict the effectiveness of these conjugate vaccines and to ensure that they cover the most prevalent circulating serotypes.

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STREPTOCOCCUS PNEUMONIAE WITH REDUCED SUSCEPTIBILITY TO PENICILLIN G — BRITISH COLUMBIA

Three cases of pneumococcal pneumonia with reduced susceptibility to penicillin G occurred in a long-term care facility in British Columbia.

The first case occurred in a 91-year-old male resident of the facility in March 1994. The patient was admitted to an acute care hospital with a diagnosis of pneumonia and pleurisy. *Streptococcus pneumoniae* was isolated from the patient's blood and found to be penicillin-resistant using a 1 µg oxacillin disk screen (a modified Kirby-Bauer test manufactured by Oxoid). The patient was subsequently treated. He recovered from his pneumonia and was sent back to the long-term care facility.

The next two cases occurred in October 1994. The first of these was a 69-year-old female resident of the facility who was admitted to the same acute care hospital on 13 October 1994 with a diagnosis of bronchopneumonia. Again, *S. pneumoniae* was isolated from the patient's blood and found to be penicillin-resistant using the oxacillin disk. The minimum inhibitory concentration (MIC) for the strain was 0.25 mg/L (intermediate susceptibility to penicillin at MIC 0.1 to 1.0 mg/L). The patient died on 15 October 1994 despite antibiotic treatment with ceftriaxone, erythromycin, and penicillin G.

An 89-year-old male resident of the facility was admitted to the same hospital on 28 October 1994 with bronchopneumonia. Penicillin-resistant *S. pneumoniae* was found in his blood. The MIC strain for this patient was identical to the earlier October case. The patient was treated with intravenous erythromycin with ceftriaxone added later for secondary infection. He recovered and was sent back to the nursing home on 11 November 1994.

In total, the acute care hospital has noted five cases of penicillin-resistant pneumonia since December 1993, when a male patient with metastatic lung cancer died of penicillin-resistant pneumococcal pneumonia that was thought to have been acquired in Seattle. Subsequent to his death, all positive cultures for *S. pneumoniae*, regardless of the site of the specimen, were tested for penicillin susceptibility using an oxacillin disk plate. In addition to the three cases from the long-term care facility, one unrelated case was identified in March 1994 in an HIV-positive male with pneumococcal pneumonia.

The long-term care facility has 78 regular residents and one emergency respite bed. The average age of the residents is approximately 88 years old and no resident is < 65 years of age. There was no obvious connection between the three cases. The two cases occurring in October 1994 lived in different areas of the facility. Thirty-eight residents of a nearby intermediate care facility frequently visit for such things as hairdressing and group events. The residents of the two facilities were presumed not to have received pneumococcal immunization since British Columbia does not have a provincial pneumococcal immunization program.

Communicable Disease Epidemiology Services at the British Columbia Centre for Disease Control was notified of these cases on 3 November 1994. A decision was made to initiate an immunization program for residents of both the long-term care facility and the nearby intermediate care facility. Public health nurses from the local public health unit and staff of the long-term care facility immunized 65 of the 78 residents on 8 November 1994. Eleven of the residents refused immunization, one resident was ill, and one was in hospital (the last case described above). Thirty-three of the 38 residents of the intermediate care facility were also immunized. No adverse immunization reactions were reported. Extra vaccine was kept by the facility to immunize new admissions.

On 12 December 1994, a 66-year-old male resident of the long-term care facility developed clinical pneumonia. He was hospitalized on 14 December 1994 and died on 16 December 1994. He was found to have had penicillin-resistant *S. pneumoniae*. He had received the pneumococcal vaccine on 8 November 1994 as part of the immunization of residents in the facility.

Specimens from all four cases from the facility were sent to the reference laboratory for typing. All were identified as *S. pneumoniae* serotype 9L, with intermediate resistance to penicillin.

As of September 1996, no further cases of penicillin-resistant *S. pneumoniae* had been identified in residents of the facility. New admissions are no longer being offered pneumococcal immunization.

Acknowledgement

Staff of the South Okanagan Health Unit assisted in the public health investigation of these cases and the immunization program at the long-term care facility.

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